
BEEFEAT
VERY DRY

Theme

"The broad generality of hormesis implies it is a characteristic of organisms rather than of the agents—such as abused drugs—that perturb them."

Actual Causes of Death in the United States in 1990

Cause	Deaths	
	Estimated No.*	Percentage of Total Deaths
Tobacco	400,000	19
Diet/activity patterns	300,000	14
Alcohol	100,000	5
Microbial agents	90,000	4
Toxic agents	60,000	3
Firearms	35,000	2
Sexual behavior	30,000	1
Motor vehicles	25,000	1
Illicit use of drugs	20,000	<1
Total	1,060,000	50

* Composite approximation drawn from studies that use different approaches to derive estimates, ranging from actual counts (eg. firearms) to population attributable risk calculations (eg. tobacco).

Etiology of Alcoholism

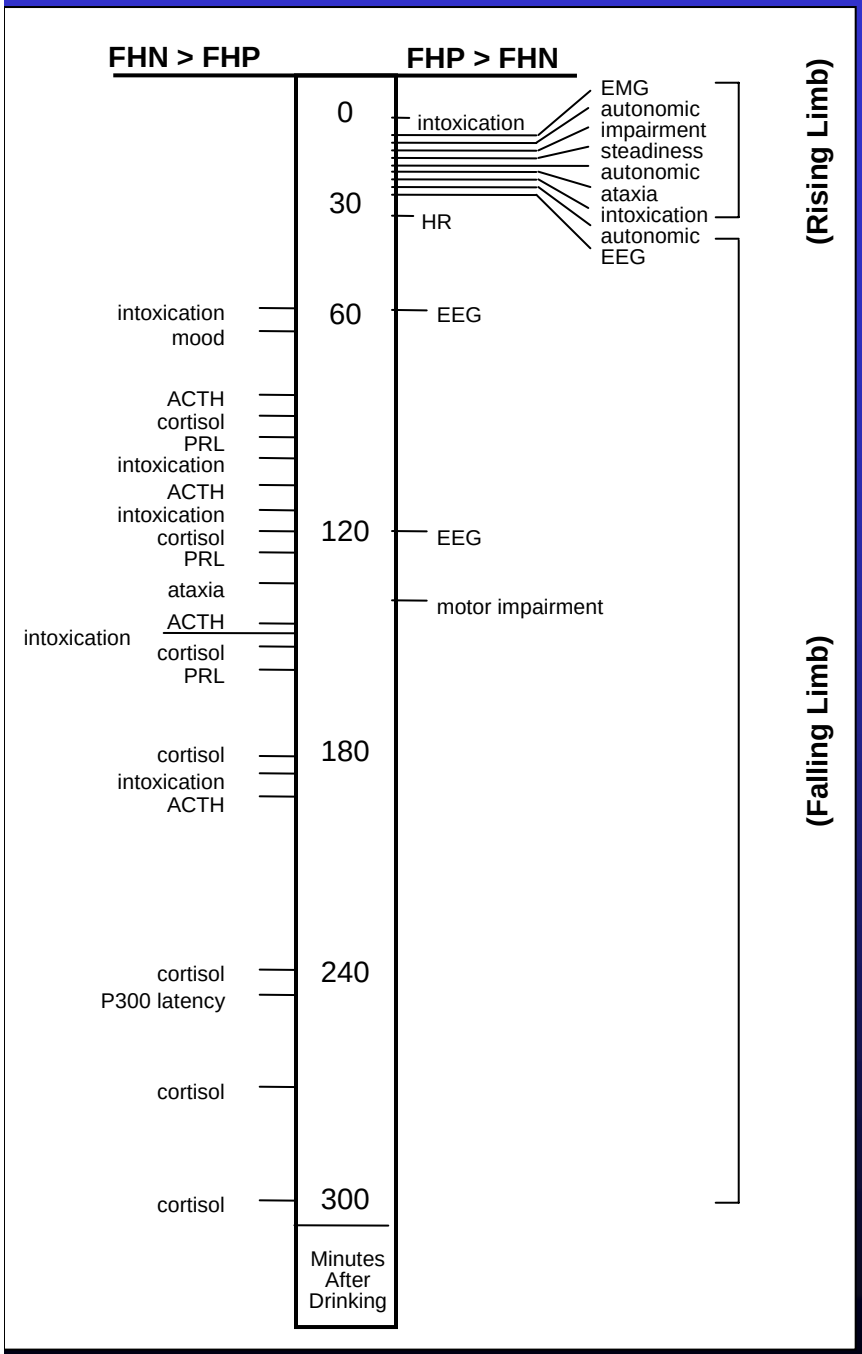
Given moderate genetic contribution to alcoholism, is there something different about the way adult offspring of alcoholics (high risk subjects) respond to a challenge dose of alcohol?

Research Question

Are individuals at elevated genetic risk for alcoholism more or less sensitive to alcohol than those at low risk?

Sensitivity can reflect:

- **"innate (alcohol naïve) sensitivity"**
- **acute tolerance/sensitization**
- **chronic tolerance/sensitization**
- **conditioned or unconditioned tolerance/ sensitization**
- **interactions with laboratory factors (e.g., stress)**

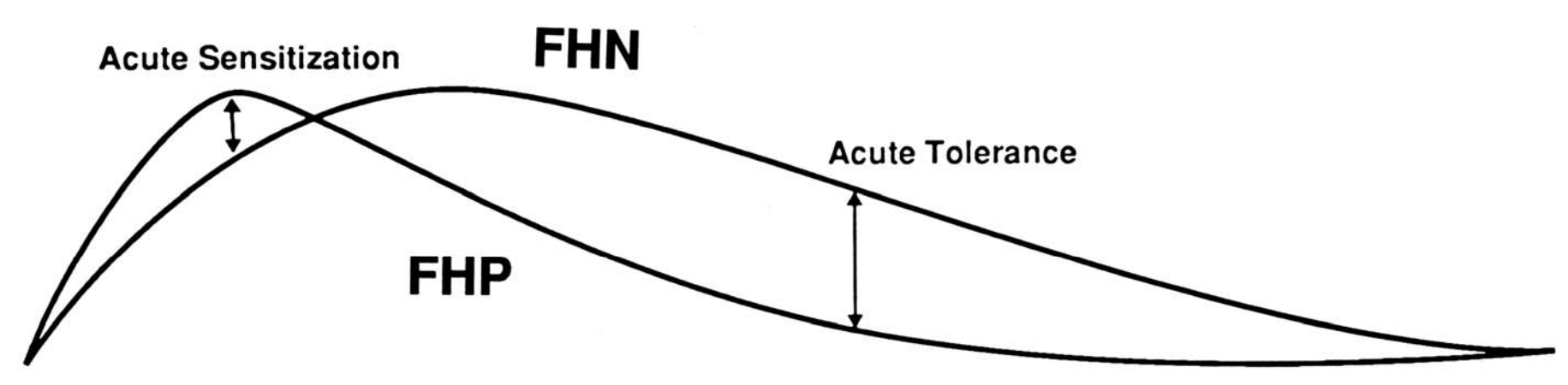


Differentiator Model

Different studies and dependent measures at various times in the breath alcohol curve. Note that high-risk groups tended to have greater responses to alcohol in the rising curve (first 30 minutes after drinking), while low-risk groups had greater responses in the falling curve (45 to 300 minutes). These results tend to support the "differentiator model" (Newlin & Thomson 1990).

Newlin & Thomson (1990)

Differentiator Model



Schematic diagram of the "differentiator model" (Newlin & Thomson 1990). Note that SOAs show an exaggerated pharmacodynamic response in the rising blood alcohol curve (i.e., acute sensitization) and an attenuated response in the falling blood alcohol curve (i.e., acute tolerance). The blood alcohol curves themselves (i.e., the pharmacokinetic response) does not differ between risk groups.

Newlin & Thomson (1990)

Differentiator Model

Rising BrAC

Positive Subjective Effects:

- euphoria
- stimulation
- locomotor activation
- loquatiousness
- sociality

Falling BrAC

Aversive Subjective Effects:

- dysphoria
- sedation
- locomotor retardation
- headache
- nausea

Newlin & Thomson (1990)

A Double Whammy

FHP sensitize in the rising BrAC limb

(positive reinforcement).

FHP accentuate the positive subjective effects in the rising BrAC limb (greater reward).

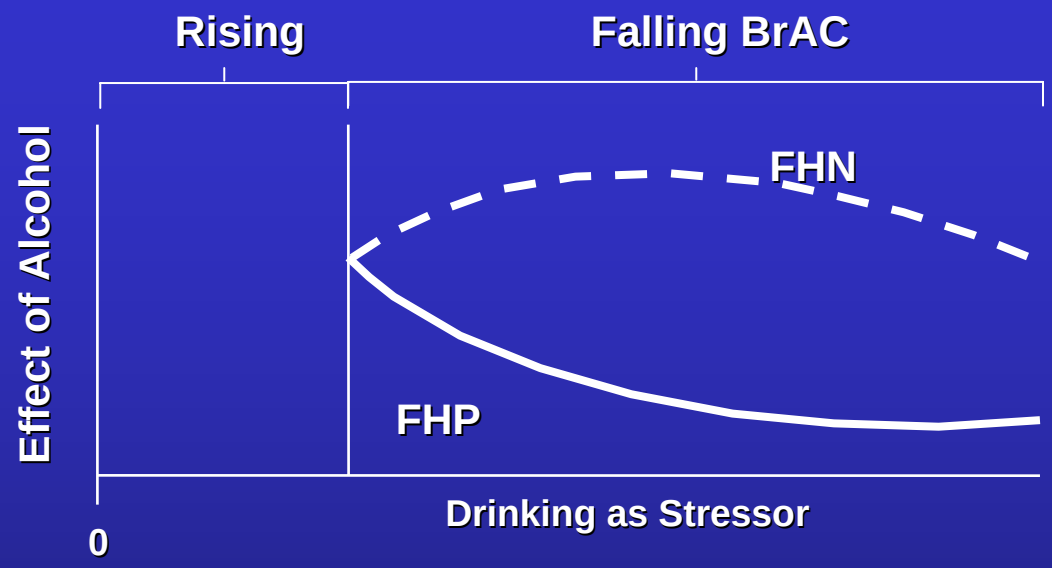
FHP more tolerant in the falling limb

(negative reinforcement).

FHP attenuate the negative subjective effects in the falling BrAC limb (less aversion)

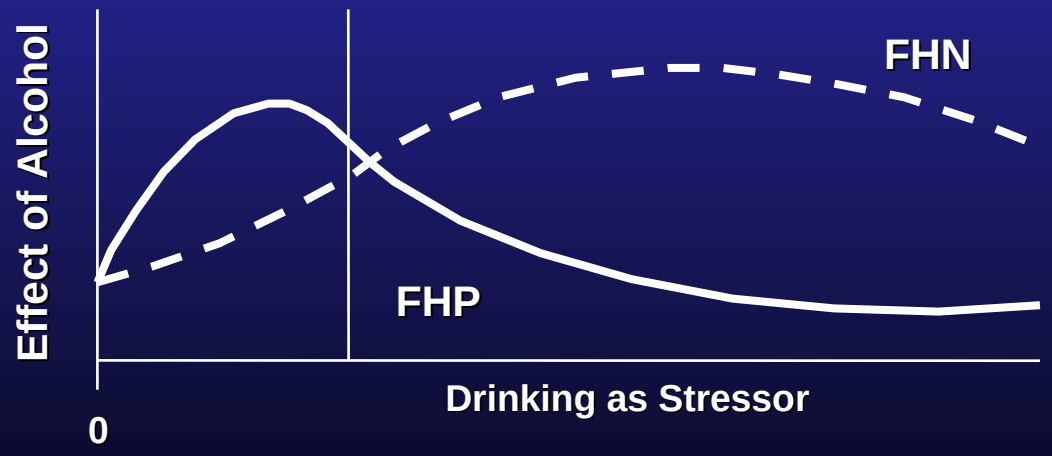
Newlin & Thomson (1990)

Difference between Models



A

Schuckit and colleagues

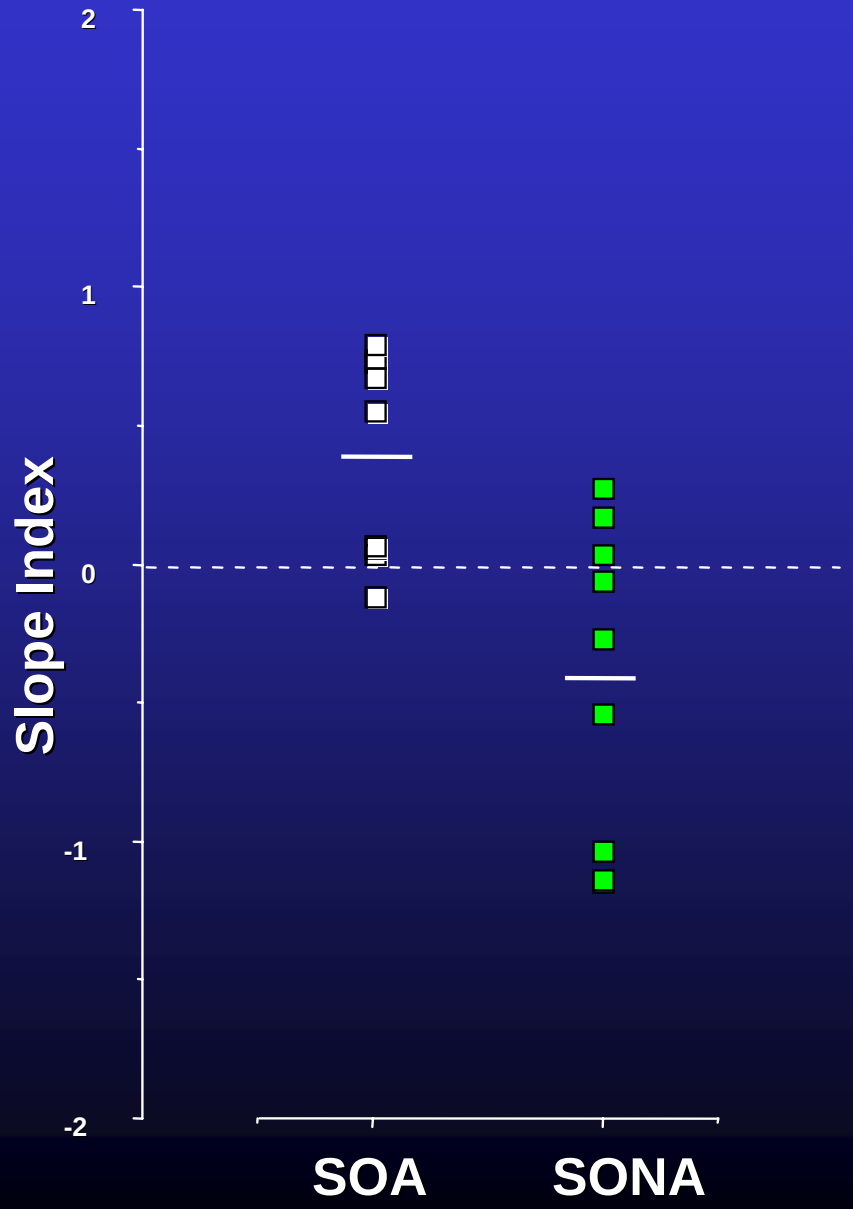


B

Differentiator Model (Newlin & Thomson, 1990)

Time after Drinking

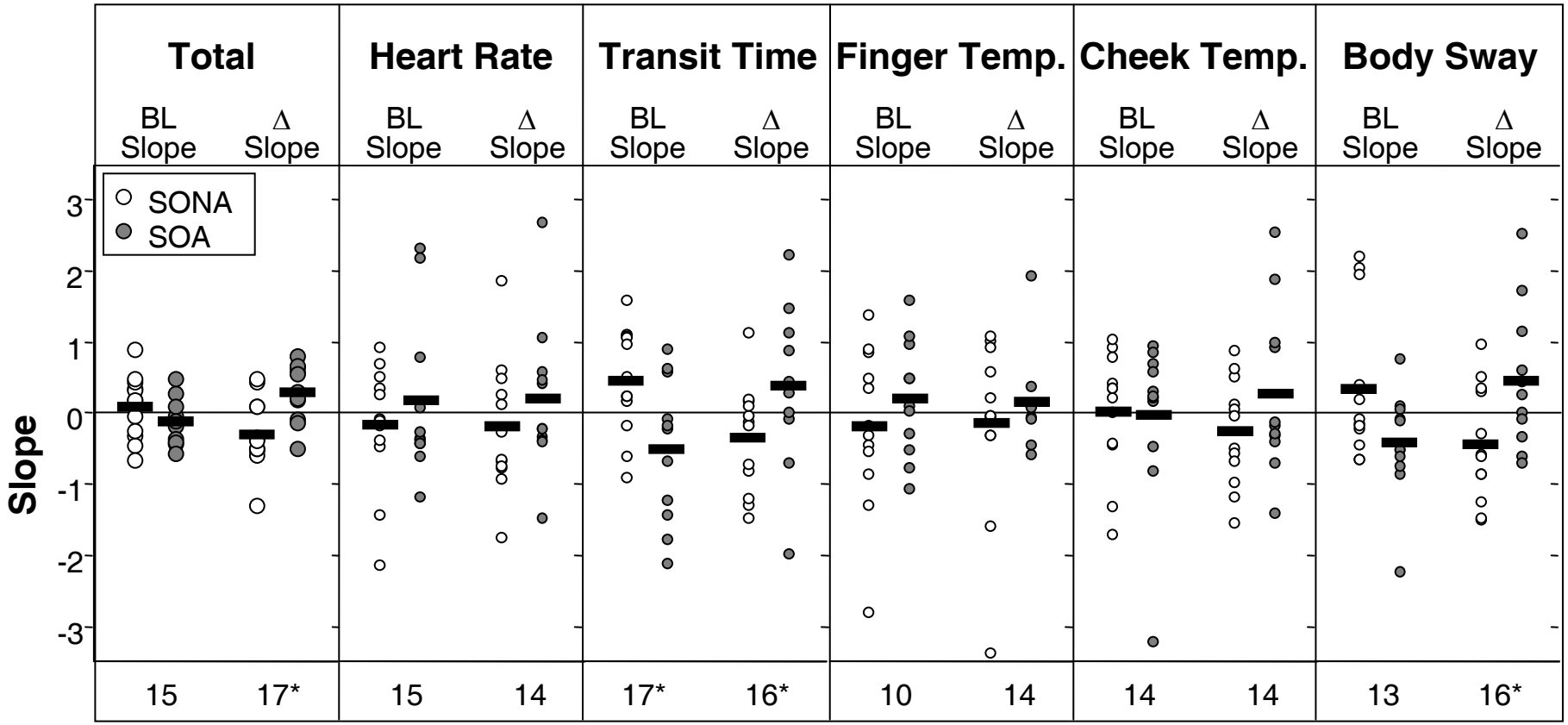
Summary Slope Scores



Transformed slope scores that quantified sensitization (positive slopes) and tolerance (negative slopes). An optimal cutoff correctly classified 15 of 18 subjects as SOA or SONA. Means are indicated by solid bars.

Newlin & Thomson (1991)

Slope Transformations in Replication Study



* p<.05

Newlin & Thomson (1999)

Limitations of Studies 1 and 2

- rising BrAC limb only
- low alcohol dose
- non-stable baselines
- limited dependent measures
  (no subjective measures)
- only one risk factor (PH+)

Schuckit's Standard Alcohol Administration Procedure

- 8:00 to 9:00 am drinking
- warm, diet soft drink mixer
- alcohol in the form of 95% USP lab ethanol
- 20% alcohol / mixer
- drinking alcohol after overnight fasting
- drinking soon after venous catheterization
- drinking alcohol in the 1st lab session

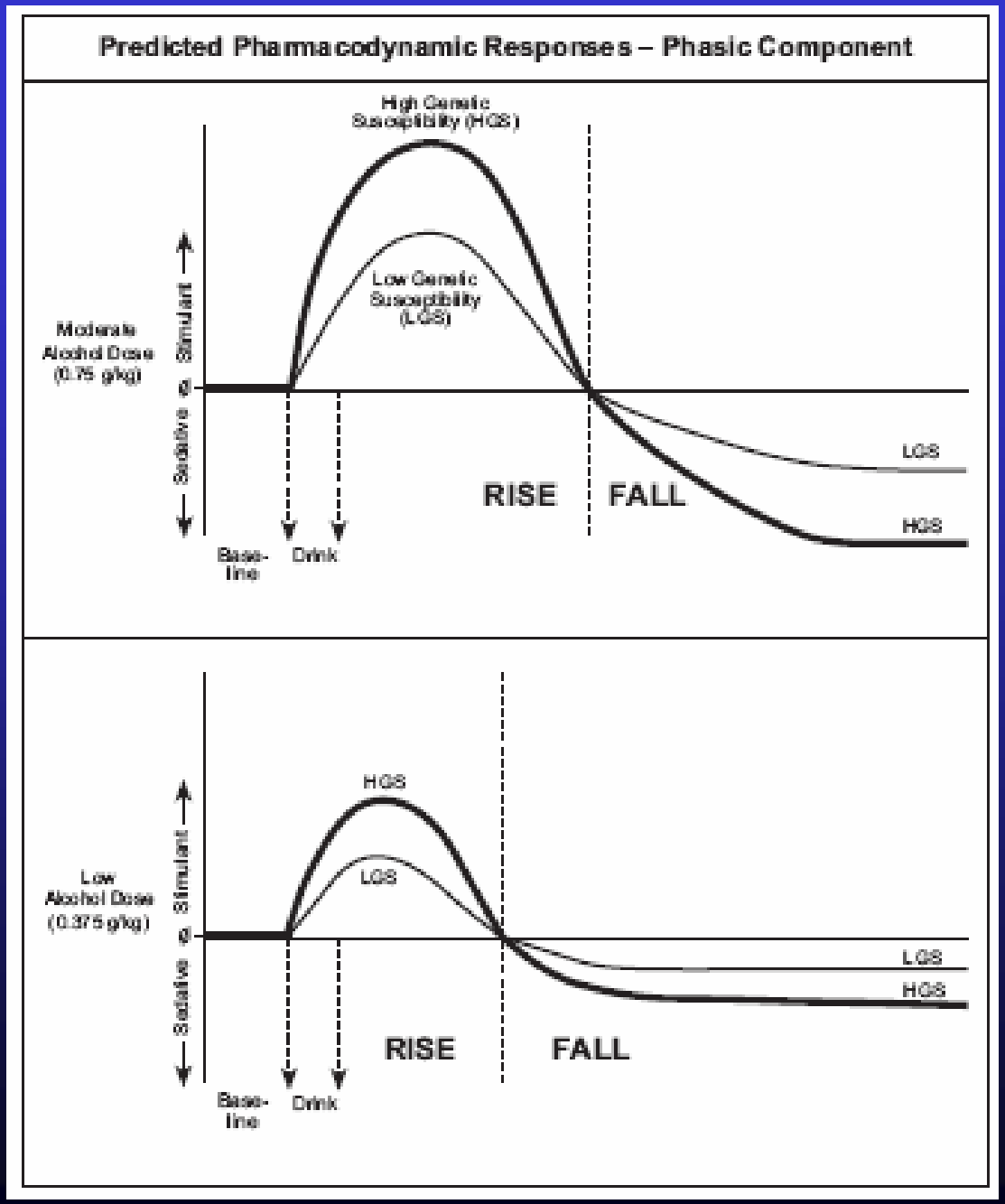
- measure "Terrible Feelings" on the SHAS

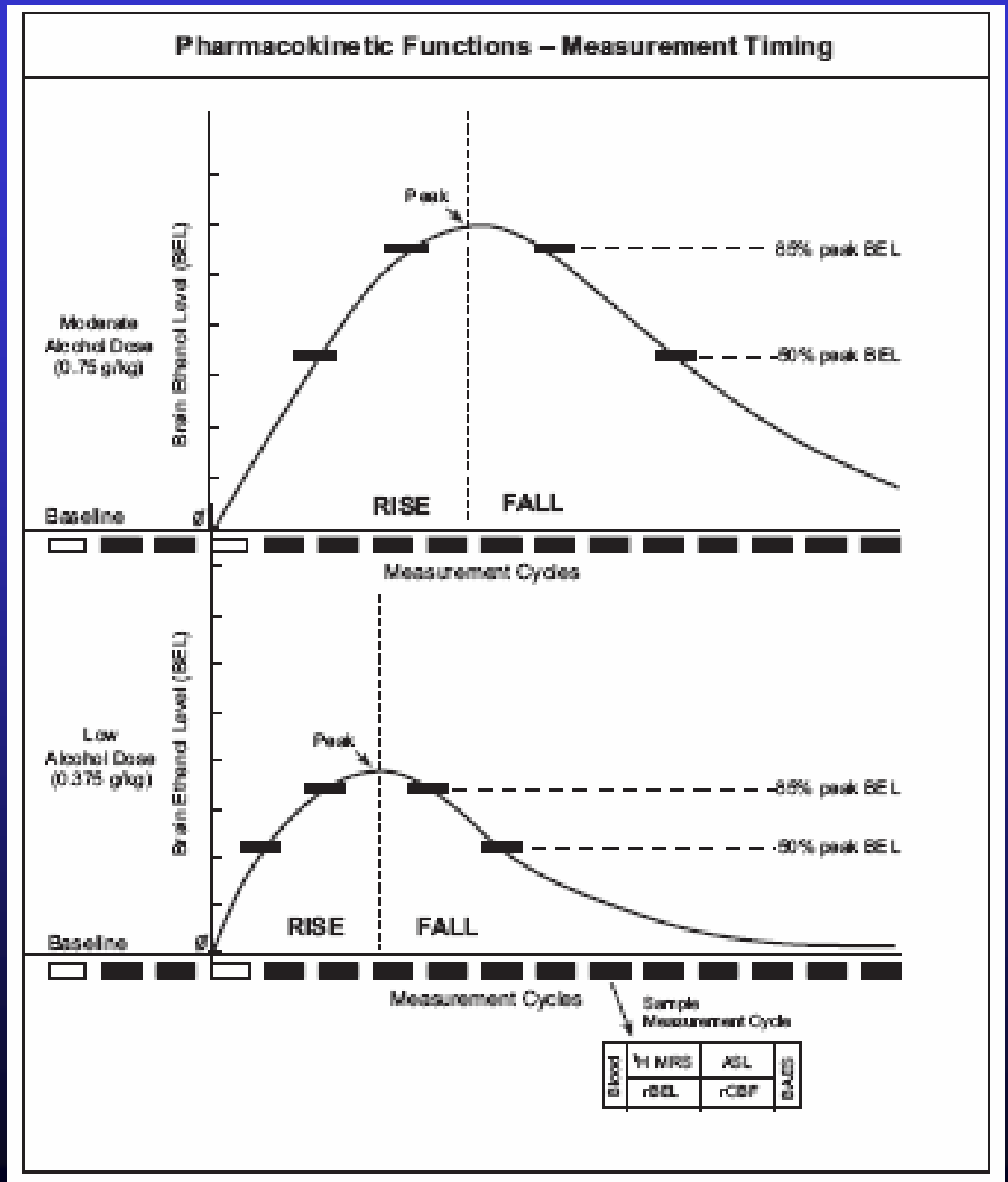
Regulated Dynamical Systems

- Strong baseline dependency is a signature of a regulated dynamical system (regulatory feedback loops)
- Hypothesis: relevant regulated system (dopamine?) is **underdamped** in FHP
- This system is more rapidly recruited and decays more quickly in FHP
- Consistent with Begleiter & Porjesz's (1999) hypothesis of CNS hyperexcitability (homeostatic imbalance) in FHP
- Stressful drinking environments exaggerate this underdamped quality

Biphasic Alcohol Response

regional brain correlates of early vs. late phases? –right vs. left hemisphere activation? –cortical vs. subcortical?	functional Magnetic Resonance Imaging (fMRI) –arterial spin labeling to measure slow responses –10's of min to hrs
high vs. low genetic risk for alcoholism?	DNA genomic susceptibility markers –from venous blood (white cells)
pharmacokinetic response clusters? –individual differences –"sharp" vs. "blunted" brain alcohol concentration curves	brain ethanol concentration –fMRI spectroscopy –completely noninvasive


Predicted Pharmacodynamic Responses – Phasic Component
High Genetic Susceptibility (HGS)
Low Genetic Susceptibility (LGS)
Moderate Alcohol Dose (0.75 g/kg)
Stimulant
0
Sedative
LGS
HGS
RISE
FALL
Base-line
Drink
Low Alcohol Dose (0.375 g/kg)
HGS
LGS
LGS
HGS
RISE
FALL
Base-line
Drink


Pharmacokinetic Functions – Measurement Timing
Moderate Alcohol Dose (0.75 g/kg)
Brain Ethanol Level (BEL)
Peak
85% peak BEL
50% peak BEL
Baseline
RISE
FALL
Measurement Cycles
Low Alcohol Dose (0.375 g/kg)
Brain Ethanol Level (BEL)
Peak
85% peak BEL
50% peak BEL
Baseline
RISE
FALL
Measurement Cycles
Sample Measurement Cycle
Blood
¹H MRS
ASL
rBEL
rCBF
BABS

Is the Alcohol Response Multiphasic?

Anticipation:

Rising BrAC curve: psychostimulant

Falling BrAC curve: psychosedative

Near Zero BrAC: acute withdrawal (hangover)


SANDWICHES
Although they restricted themselves to one drink at lunch time, Howard and Tom still found they were not at their most productive in the afternoons

Theme

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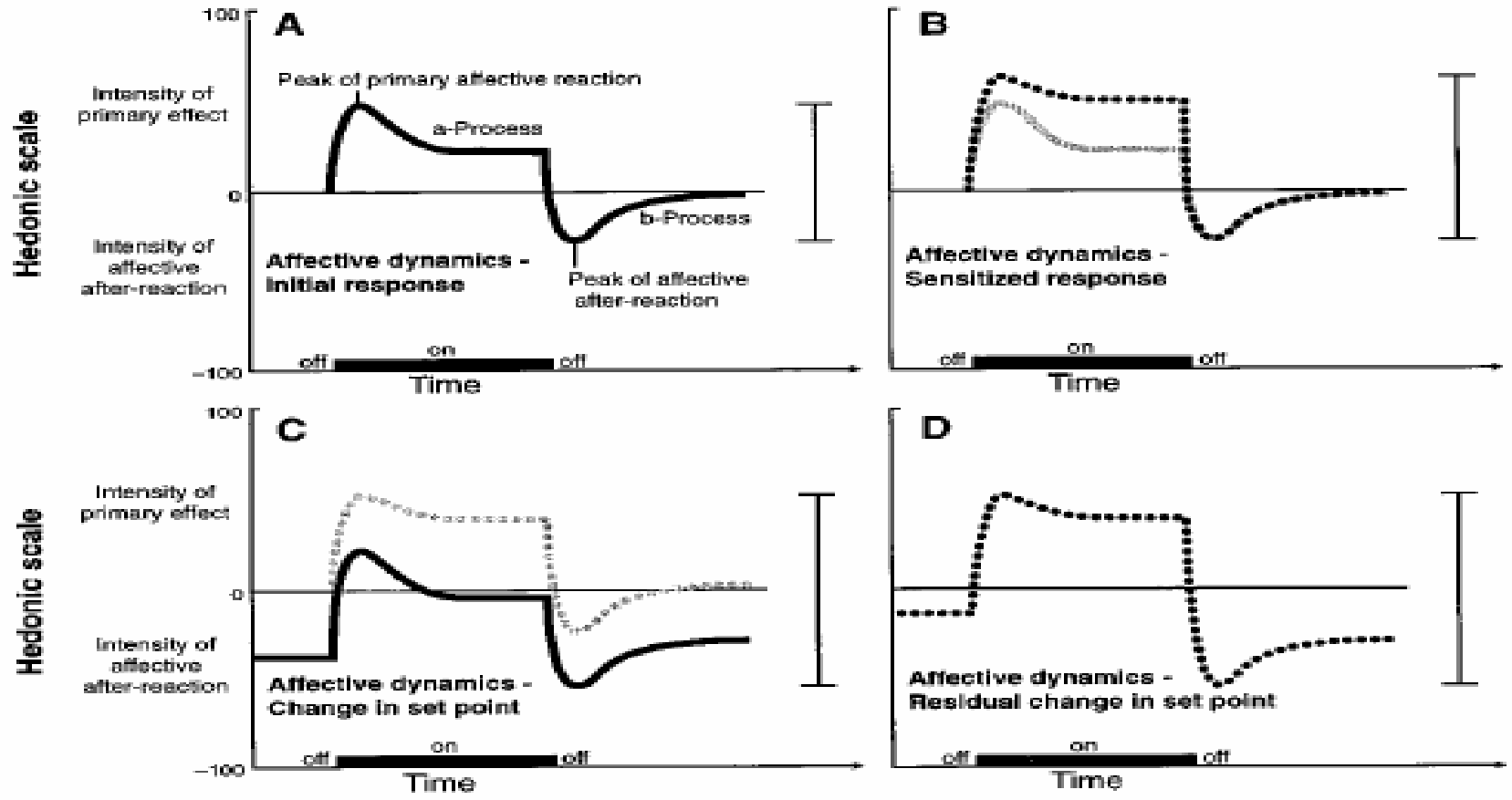
Opponent Process Theory



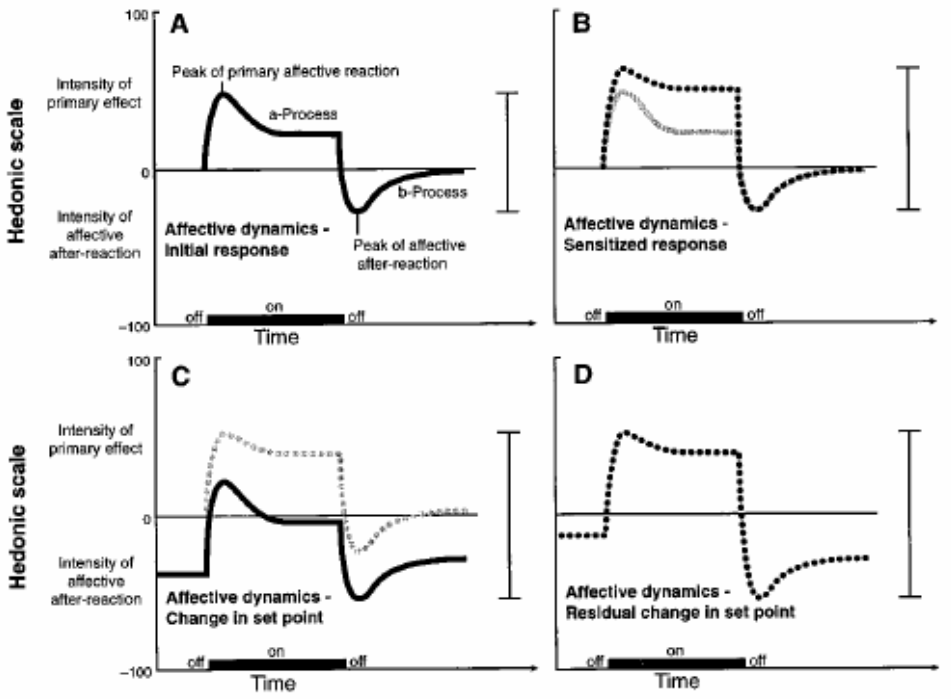


Fig. 4. Diagram illustrating an extension of Solomon and Corbit's opponent-process model of motivation to incorporate the conceptual framework of this article (*21*). All panels represent the affective response to the presentation of the stimuli (that is, drug administration). (**A**) The original description of the affective stimulus, which was argued to be a sum of both an a-process and a b-process and represents the initial experience with no prior drug history. (**B**) The same affective stimulus in an individual with an intermittent history of drug use that may result in sensitized response. The shaded line illustrates the sametrace of the initial experience in (A). The dotted line represents the sensitized response. (**C**) Change in the affective stimulus hypothesized to exist in the heavily dependent individual (that is, after chronic exposure) where there is a major change in the hedonic set point. This represents a change sufficient to be considered a major break with hedonic homeostasis. The light dotted line represents the sensitized response observed in (B). (**D**) The hypothesized state of protracted abstinence and enhanced vulnerability to relapse with a history of chronic continuous experience. The change in this panel reflects the change in the affective response in an organism with a history of depen-dence where there is both a change in set point that is long-lasting and a residual sensitization. The bar to the right of each diagram illustrates the total peak-to-peak contrast between the lowest point in negative affect to the highest point in positive mood produced by a drug at any point in the addiction cycle. An alternative hypothesis still under consideration is that even during an intermittent sensitization pattern of drug-taking, the affective after-reaction (b-process) also may get progressively larger and larger (*21*). "On" refers to the "time on" of the hedonic stimulus, in this case the drug action. "Off" refers to the "offset" of the drug action.

Parallels

Hormesis (dose and temporal hormesis)	Opponent Process Theory (Pavlovian Drug Conditioning)
ADAPTIVE	ADAPTIVE
brain processes	hedonic processes
initial stimulation, then inhibition/impairment	“a” process & “b” process
“nonadditivity” of processes	“nonadditivity” of processes
conditionability	conditionability
tolerance (and sensitization?)	tolerance and sensitization
strong empirical base	strong empirical base
motivation?	motivation

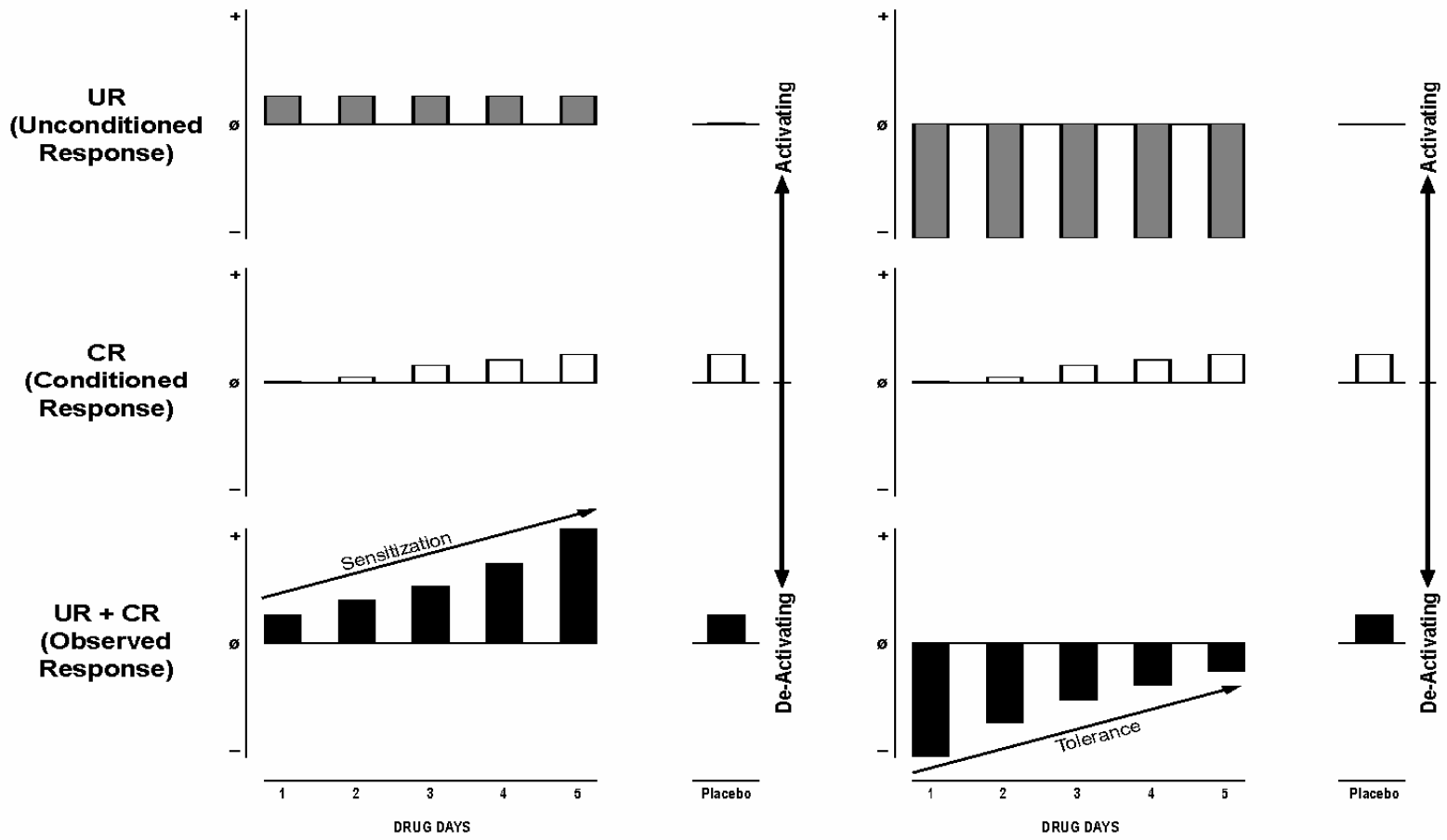
Pavlovian Drug Conditioning

	DIRECTION	FUNCTION
Conditioned Response (CR)	always activating	anticipatory
Unconditioned Response (UR)	de-activating	drug effect
Unconditioned Response (UR)	activating	drug effect
	INTERACTION	RESULT
CR + de-activating UR	inhibitory (sub-additive)	conditioned tolerance
CR + activating UR	synergistic (super-additive)	conditioned sensitization

Activation Dimension

Activating Drug Effects	De-Activating Drug Effects
Nonhuman Animals	Nonhuman Animals
locomotor act.	locomotor de-act.
hyperthermia	hypothermia
hyperalgesia	hypoalgesia
Human	Human
motor act.	motor de-act.
loquatiousness	verbal inhibition
hypervigilance	sedation
autonomic act.	autonomic de-act.

Conditioned Tolerance and Sensitization



What's in a Response?

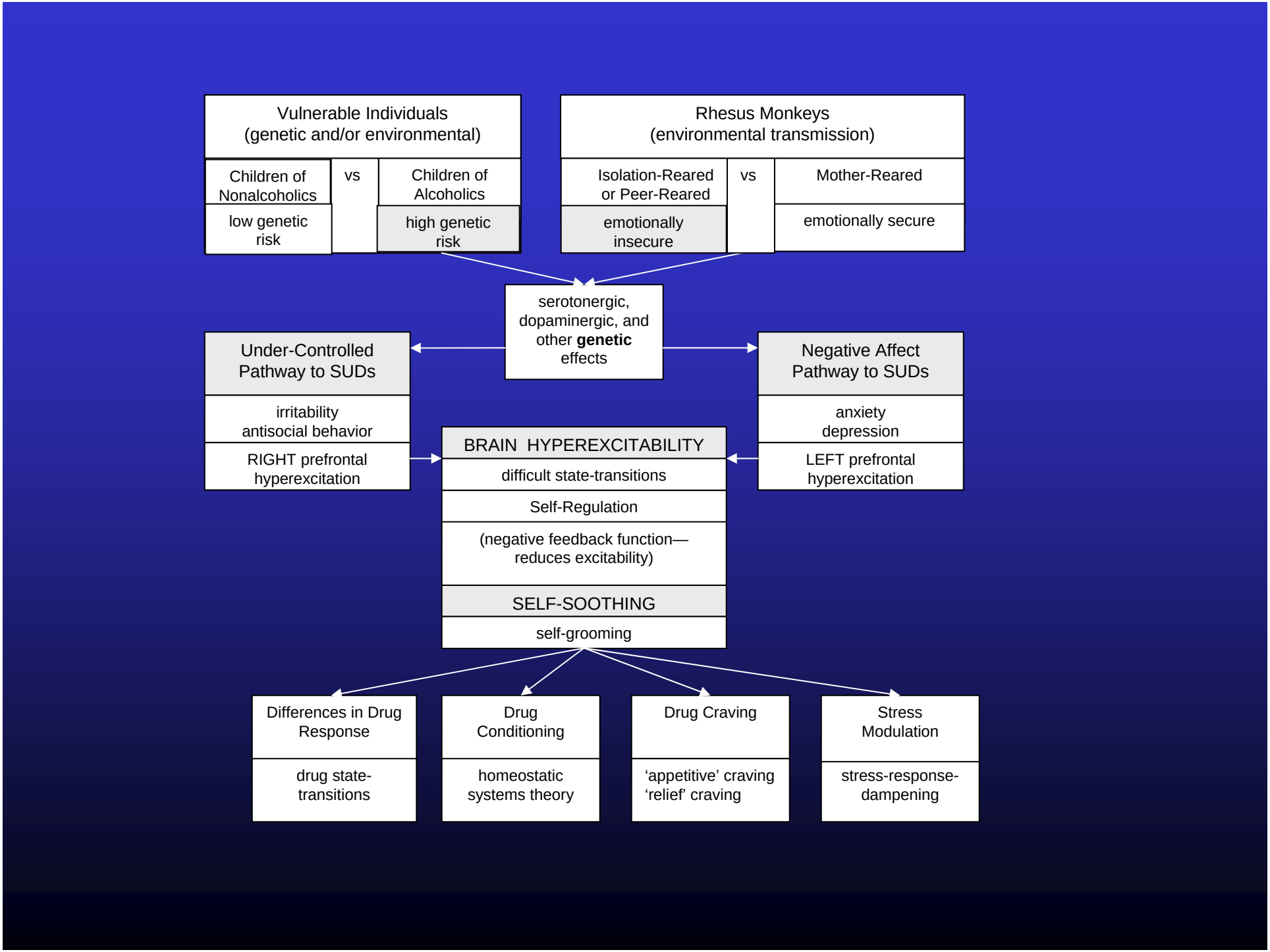
- Is an hormetic response composed of one process, two processes, three processes, etc.?
- If the hormetic response encompasses multiple processes, how do these processes interact with each other?

Plausible Hypothetical Assumptions

- Hormetic (biphasic) drug response has both a psychostimulant and a psychosedative component.
- The psychostimulant component is recruited rapidly and is roughly linear with dose.
- The psychosedative component is recruited slowly and is exponentially related to dose.
- These two components are nonadditive.
- Do these assumptions “generate” dose-hormesis and temporal-hormesis?

A Candidate Mechanism?

	LEFT Prefrontal	RIGHT Prefrontal
Cognition	visuospatial	expressive speech
Emotion	positive affect (plus anger)	negative affect (except anger)
Motivation	approach	withdrawal
Risk Pathway	under-controlled	negative affectivity


Vulnerable Individuals
(genetic and/or environmental)
Children of Nonalcoholics
low genetic risk
vs
Children of Alcoholics
high genetic risk
Rhesus Monkeys
(environmental transmission)
Isolation-Reared or Peer-Reared
emotionally insecure
vs
Mother-Reared
emotionally secure
serotonergic, dopaminergic, and other genetic effects
Under-Controlled Pathway to SUDs
irritability
antisocial behavior
RIGHT prefrontal hyperexcitation
Negative Affect Pathway to SUDs
anxiety
depression
LEFT prefrontal hyperexcitation
BRAIN HYPEREXCITABILITY
difficult state-transitions
Self-Regulation
(negative feedback function—reduces excitability)
SELF-SOOTHING
self-grooming
Differences in Drug Response
drug state-transitions
Drug Conditioning
homeostatic systems theory
Drug Craving
'appetitive' craving
'relief' craving
Stress Modulation
stress-response-dampening

Control Theory and Hormesis

A promise as yet unfulfilled?

Albert Einstein

"If at first the idea is not absurd, then there is no hope for it."


Hormesis 'R' Us